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EFFECT OF DRUGS ON RESPONSE-DURATION DIFFERENTIATION VII: RESPONSE-FORCE REQUIREMENTS

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Rats were trained to press a lever for at least 1 s but for less than 1.3 s. The force required to press the lever was then increased or decreased by 10, 15, or 20 g. Increases in the force requirements for lever pressing decreased timing accuracy, but decreases in the force requirement had the opposite effect. Accuracy decreases at increasing force requirements were characterized by an increase in the relative frequency of responses that were too short to meet the reinforcement criterion. In contrast, increases in accuracy when the force requirements were decreased were characterized by increases in response durations that met the reinforcement criterion and decreases in the relative frequency of responses that were too short to produce the reinforcer. Phencyclidine (PCP) and methamphetamine produced dose-dependent decreases in accuracy that were associated primarily with increases in the relative frequency of short response durations, although methamphetamine also produced increases in long response durations at some doses. When the effects of PCP were determined with the force requirement increased by 10 g or decreased by 15 g, the cumulative response-duration distribution shifted toward even shorter response durations. When the effects of methamphetamine were determined with the force requirement on the lever increased by 10 g, the cumulative frequency distribution was shifted toward shorter response durations to about the same extent as it had been before force requirements increased; however, when the force required to press the lever was decreased by 15 g, these shifts toward shorter response durations almost completely disappeared. These results show that increases and decreases in the force requirements for lever pressing have different effects on the accuracy of temporal response differentiation.

Key words: temporal response differentiation, methamphetamine, phencyclidine, response force, lever press, rat

Many drugs alter timing behavior and thereby potentially affect behavior that requires accurately timed responses. Some investigators have studied the effects of drugs on timing behavior using schedules of reinforcement that reinforce temporally spaced responding, but in general these investigators have used schedules that require that responses be spaced more than 10 s apart (Li, Marek, Hand, & Seiden, 1990; Marek, Li, & Seiden, 1989; Marek & Seiden, 1988; McGuire & Seiden, 1980; O'Donnell & Seiden, 1983). Fewer investigators have studied the effects of drugs on shorter, precisely timed responses. Some years ago, a procedure for studying temporal response differentiation (TRD) was developed (McMillan & Patton, 1965). These TRD schedules require not only that the subject hold down a lever for a minimum time period but also that the lever be released before a maximum time period has elapsed. Temporal response differentiation schedules that reinforce only these precisely timed responses recently have been used to study the effects of the drugs of abuse on timing behavior (Hudzik & McMillan, 1994a, 1994b; McClure, Wenger, & McMillan, 1997; McMillan, Adams, Wenger, McClure, & Hardwick, 1994; Schulze et al., 1988; Schulze & Paule, 1990, 1991; Schulze, Slikker, & Paule, 1989).

Under the TRD schedule used in this study, the reinforcer was delivered following a continuous lever press that was at least 1.0 s in duration but not longer than 1.3 s. In previous studies using a TRD 1–1.3-s schedule in which the reinforcer was delivered following a continuous lever press that was at least 1.0 s in duration but not longer than 1.3 s, both methamphetamine and phencyclidine (PCP) decreased the percentage of responses that

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were reinforced. However, methamphetamine flattened the relative response-duration distributions at doses of 3.0 mg/kg or greater (Hudzik & McMillan, 1994a; McClure et al., 1997; McMillan et al., 1994) by increasing the proportions of response durations that were either too short or too long to produce a reinforcer. In contrast to methamphetamine, PCP increased the relative frequency only of response durations that were too short to produce the reinforcer (Hudzik & McMillan, 1994a; McClure et al., 1997; McMillan et al., 1994).

Methamphetamine and PCP also decreased accuracy under TRD schedules requiring longer response durations for food presentation (McClure et al., 1997). Under these two separate TRD schedules, the reinforcer was delivered following a continuous lever press that was at least 4.0 s in duration but not longer than 5.2 s, or following a continuous lever press that was at least 10 s in duration but not longer than 13 s. In contrast to the effects of these drugs on responding under the TRD 1–1.3-s schedule, the effects of methamphetamine and PCP on the relative frequency distributions of response durations under longer TRD schedules were very similar. Because these drugs produce different effects under the TRD 1–1.3-s schedule than under TRD schedules with longer timing requirements, performance under these schedules may involve different behavioral mechanisms. Under a TRD 1–1.3-s schedule, the animal must release the lever within a 300-ms period after 1 s has elapsed, and these precisely timed responses may require motor skills not required under longer TRD schedules.

As a continuation of studies of the effects of methamphetamine and PCP on responding under TRD schedules, we determined whether the differential effects of these drugs seen under the TRD 1–1.3-s schedule were altered by changes in lever-force requirements. It was reasoned that under the TRD schedule, the animal makes a precise motor response to meet the timing requirements of the schedule. Changes in the force requirements for lever presses would be likely to disrupt performance under the TRD schedule and perhaps differentially modify the effects of drugs on responding under this schedule.

METHOD

Subjects

Four male Sprague-Dawley rats that had been used in a previous experiment (McMillan et al., 1994) were used. The rats weighed 315 to 320 g at 80% of free-feeding weights. They were maintained at these weights by food presented during the session and by supplemental feeding after the test sessions. Rats were housed individually in suspended stainless-steel cages in a colony room maintained at 70 to 74 °F with a 12:12 hr light/dark cycle (lights on 6:00 a.m. to 6:00 p.m.) during the initial training period. Water was available at all times except during the experimental sessions.

Apparatus

Each rat was trained and tested in a different two-lever chamber (Gerbrands Model G7410) encased in a different sound-attenuating Gerbrands enclosure (Model G7210). A Gerbrands feeder delivered 97-mg Noyes food pellets into a food cup mounted between the levers when schedule contingencies had been met. A houselight and a stimulus light consisting of 28-V DC bulbs were mounted in the ceiling of the experimental chamber and above the right lever. A downward force sufficient to close the microswitch contact on the right lever (Gerbrands Model G6312) activated the stimulus light and produced a continuous tone (Sonalert Model SC628H in series with a 15-kΩ resistor) when microswitch contacts were closed. The forces in newtons (measured in grams on a dynamometer) that were required to close the microswitch when the lever was pressed were 0.37 N (38 g) for Rat 402 in Chamber 1, 0.25 N (25 g) for Rat 405 in Chamber 2, 0.30 N (31 g) for Rat 408 in Chamber 3, and 0.32 N (33 g) for Rat 413 in Chamber 4. Because the dynamometer readings were in grams, lever-force requirements will be specified in grams hereafter. The force required to close the microswitch was not equalized across chambers because the experiments being conducted by other investigators using the same chambers might be disrupted. Events in the chambers were controlled and data collected using a Firestar 386 computer with a Med Associates interface housed in a separate room.

Table 1

Sequence order of force changes for each rat.

	Force changes (in grams)					
Rat	1	2	3	4	5	6
402	+10	−10	+20	−20	+15	−15
405	+10	−10	+20	−20	+15	−15
408	−10	+10	−20	+20	−15	+15
413	−10	+10	−20	+20	−15	+15

Training Procedure

The training of these rats has been described in detail previously (McMillan et al., 1994). Briefly, the rats were trained to press the lever on the right side of the chamber with sufficient force to close the microswitch to deliver a food pellet (hereafter the term *lever press* will imply a response with sufficient force to close the microswitch). Once the rat consistently pressed the lever, the response duration required to produce a pellet was gradually lengthened to 1.0 s in 0.3-s increments, with a final increment of 0.1 s. Under this procedure, responses were reinforced only if their duration exceeded the minimum time requirement required by the schedule. Once this 1.0-s minimum hold had been established, the upper limit of the response duration below which the reinforcer could be produced was gradually reduced. Under the final TRD schedule, only lever presses at least 1 s but less than 1.3 s in duration were reinforced. The session ended with the delivery of 50 reinforcers or after 40 min, whichever occurred first.

Force Variation Procedure

The baseline force on the lever that was necessary to close the microswitch as measured by the dynamometer was 25 g to 38 g depending on the chamber. In each chamber during six different test sessions, washers were added or removed on the side of the fulcrum located behind the test chamber wall to change the force required to activate the microswitch by +10, +15, +20, −10, −15, or −20 g. All rats were tested once at each of six different force requirements in the order shown in Table 1. Sessions were conducted Mondays through Fridays between 7:30 a.m. and 9:30 a.m., with force requirements changed only on Tuesdays and Fridays. The force required during training sessions will be referred to as the baseline force requirement in these experiments.

Table 2

Sequence of drug–force combinations for each rat.

	Rat 402	Rat 405	Rat 408	Rat 413
Series 1 (−15 g force)				
1	5.6 MAP	5.6 MAP	0.3 MAP	0.3 MAP
2	3.0 MAP	3.0 MAP	1.0 MAP	1.0 MAP
3	1.0 MAP	1.0 MAP	3.0 MAP	3.0 MAP
4	0.3 MAP	0.3 MAP	5.6 MAP	5.6 MAP
Series 2 (−15 g force)				
1	0.3 PCP	0.3 PCP	3.0 PCP	3.0 PCP
2	1.0 PCP	1.0 PCP	1.7 PCP	1.7 PCP
3	1.7 PCP	1.7 PCP	1.0 PCP	1.0 PCP
4	3.0 PCP	3.0 PCP	0.3 PCP	0.3 PCP
Series 3 (+10 g force)				
1	3.0 PCP	3.0 PCP	5.6 MAP	5.6 MAP
2	1.7 PCP	1.7 PCP	3.0 MAP	3.0 MAP
3	1.0 PCP	1.0 PCP	1.0 MAP	1.0 MAP
4	0.3 PCP	0.3 PCP	0.3 MAP	0.3 MAP
Series 4 (+10 g force)				
1	0.3 MAP	0.3 MAP	0.3 PCP	0.3 PCP
2	1.0 MAP	1.0 MAP	1.0 PCP	1.0 PCP
3	3.0 MAP	3.0 MAP	1.7 PCP	1.7 PCP
4	5.6 MAP	5.6 MAP	3.0 PCP	3.0 PCP

Note. MAP = methamphetamine; PCP = phencyclidine.

Drugs and Testing

For determination of dose–effect curves with baseline force requirements, doses of methamphetamine sulfate (Sigma Chemical Co.) and phencyclidine hydrochloride (National Institute on Drug Abuse) were given in ascending dose order, except that Rats 405 and 413 received the lowest dose last. Both PCP (0.3, 1.0, 1.7, or 3.0 mg/kg) and methamphetamine (0.3, 1.0, 3.0, or 5.6 mg/kg) were dissolved in physiologic saline and administered intraperitoneally in a volume of 1 ml/kg, 10 min prior to the beginning of sessions. All dose levels are expressed as the salts. Methamphetamine, PCP, or saline was administered on Tuesdays and Fridays. Table 2 shows the order of exposure to the different force requirements when the effects of drugs were studied.

Data Analysis

The total number of responses emitted, response rate (responses per second), accuracy (reinforced responses divided by total responses), and mean response duration were calculated for every session for each rat.

Table 3

Performance indicators for responding under the TRD 1.0–1.3 s schedule at different force requirements.

	Rat 402			Rat 405		
Treatment	Responses	Response rate	Accuracy	Responses	Response rate	Accuracy
−20 g	57	0.06	87.7	64	0.08	78.1
−15 g	68	0.06	73.5	67	0.09	74.6
−10 g	73	0.07	68.5	75	0.08	66.7
Baseline	101.3 ± 7.9	0.11 ± 0.01	49.6 ± 4.0	75.7 ± 3.5	0.09 ± 0.01	66.2 ± 3.0
+10 g	116	0.10	43.1	83	0.09	60.2
+15 g	167	0.12	29.6	110	0.12	45.5
+20 g	207	0.17	24.2	125	0.14	40.0

Note. The total number of responses emitted, accuracy (% reinforced responses), and response rate (responses per second) are based on single observations in each of 4 rats. The baseline level is an average of 10 daily training sessions during the experimental periods. Baseline data include standard deviations.

Mean curves were plotted for accuracy as a function of the force required to press the lever, and data from individual animals were presented in tables. Mean dose–response curves for the effects of PCP and methamphetamine on accuracy were also plotted, and the data from individual animals were presented in tables. Pearson product-moment correlation coefficients (r) relating accuracy to response rate were calculated by correlating accuracy with response rates in individual animals from the data in Tables 3 through 5.

Each response, depending on its duration, was collected into one of 24 consecutive time bins. Each of the first 23 time bins was 0.1 s wide. All response durations less than 0.1 s were cumulated in Bin 1, all response durations of at least 0.1 s but less than 0.2 s were

Table 4

Effect of phencyclidine and force changes on performance indicators in individual rats. The number of responses emitted, response rate (responses per second), and accuracy (% reinforced responses) for PCP alone and PCP combined with force changes. Each value for the saline days represents an average of three sessions with standard deviations. Drug data represent single observations in each rat.

	Rat 402			Rat 405		
Dose	Responses	Response rate	Accuracy	Responses	Response rate	Accuracy
Baseline						
Saline	88.7 ± 20.5	0.09 ± 0.02	58.5 ± 14.0	88.0 ± 7.5	0.09 ± 0.01	57.1 ± 4.8
PCP 0.3	110	0.10	45.5	88	0.09	56.8
PCP 1.0	91	0.11	55.0	174	0.17	28.7
PCP 1.7	131	0.13	38.2	322	0.22	15.5
PCP 3.0	334	0.24	15.0	420	0.23	10.5
−15 g force						
Saline	70.0 ± 11.3	0.08 ± 0.02	72.6 ± 10.7	60.7 ± 3.5	0.08 ± 0.002	82.6 ± 4.8
PCP 0.3	106	0.11	47.2	80	0.11	62.5
PCP 1.0	127	0.13	39.4	126	0.13	39.7
PCP 1.7	124	0.14	40.3	316	0.18	10.8
PCP 3.0	290	0.16	4.5	1	0.001	—[a]
+10 g force						
Saline	127.0 ± 10.8	0.12 ± 0.02	39.0 ± 3.3	85.3 ± 9.1	0.10 ± 0.01	59.0 ± 6.2
PCP 0.3	148	0.15	33.8	86	0.10	58.1
PCP 1.0	174	0.19	28.7	159	0.18	31.5
PCP 1.7	168	0.18	29.8	129	0.16	38.8
PCP 3.0	58	0.03	0.0	43	0.02	7.0

[a] These responses were not used for relative cumulative frequency distributions because fewer than 25 responses were emitted.

Table 3
(*Extended*)

Rat 408			Rat 413		
Responses	Response rate	Accuracy	Responses	Response rate	Accuracy
66	0.07	75.8	76	0.09	65.8
79	0.10	63.3	82	0.10	61.0
93	0.10	53.8	104	0.10	48.1
96.1 ± 6.5	0.10 ± 0.01	52.3 ± 3.7	100.2 ± 10.5	0.11 ± 0.02	50.4 ± 5.2
120	0.12	41.7	124	0.14	40.3
364	0.23	13.7	239	0.13	20.1
121	0.07	2.5	331	0.18	15.1

cumulated in Bin 2, and so on. Response durations of 2.3 s and longer were collected in the 24th bin. Bins 11, 12, and 13 collected response durations that produced the reinforcer. The relative frequency of responses in each time bin (the number of responses collected in each bin divided by the total number of responses made during the session) was calculated for each individual rat for each session. These cumulative frequencies were plotted as sigmoidal curves to analyze the response-duration distributions. If animals failed to respond at least 25 times within a session, the data were used only to calculate response rates and were not used to plot response-duration distributions.

RESULTS

Baseline accuracy (percentage of total responses with durations of at least 1.0 s but less than 1.3 s) was close to 50% for 3 of the rats

Table 4
(*Extended*)

Rat 408			Rat 413		
Responses	Response rate	Accuracy	Responses	Response rate	Accuracy
101.0 ± 5.3	0.12 ± 0.01	49.6 ± 2.7	91.0 ± 1.0	0.14 ± 0.01	55.0 ± 0.6
124	0.19	40.3	96	0.14	52.1
132	0.16	37.9	105	0.15	47.6
188	0.27	26.6	125	0.17	40.0
241	0.26	20.8	161	0.18	31.1
67.0 ± 1.7	0.08 ± 0.01	74.7 ± 1.9	78.0 ± 11.5	0.08 ± 0.04	61.6 ± 6.3
62	0.08	80.7	73	0.10	68.5
97	0.12	51.6	109	0.15	45.9
202	0.21	24.8	382	0.24	13.1
396	0.22	10.6	226	0.13	15.0
100.7 ± 19.9	0.12 ± 0.01	51.1 ± 10.9	114.7 ± 8.6	0.15 ± 0.02	43.8 ± 3.2
159	0.18	31.5	115	0.18	43.5
440	0.35	11.4	157	0.22	31.9
560	0.31	1.4	166	0.23	30.1
34	0.02	2.9	264	0.15	9.5

Table 5

Effect of methamphetamine (MAP) and force changes on performance indicators in individual rats. The number of responses emitted, response rate, and accuracy for MAP doses alone and MAP combined with force changes. Each value for the saline days represents an average of three sessions with standard deviations. Drug data represent single observations in each rat.

	Rat 402			Rat 405		
Dose	Responses	Response rate	Accuracy	Responses	Response rate	Accuracy
Baseline						
Saline	88.7 ± 20.5	0.09 ± 0.02	58.5 ± 14.0	88.0 ± 7.5	0.09 ± 0.01	57.1 ± 4.8
MAP 0.3	112	0.10	44.6	126	0.13	39.7
MAP 1.0	122	0.15	41.0	116	0.17	43.1
MAP 3.0	150	0.08	11.3	127	0.07	34.7
MAP 5.6	0	0.00	—[a]	0	0.00	—[a]
−15 g force						
Saline	70.0 ± 11.3	0.08 ± 0.02	72.6 ± 10.7	60.7 ± 3.5	0.08 ± 0.002	82.6 ± 4.8
MAP 0.3	87	0.11	57.5	76	0.13	65.8
MAP 1.0	74	0.09	67.6	61	0.09	82.0
MAP 3.0	72	0.08	69.4	70	0.09	71.4
MAP 5.6	0	0.000	—[a]	0	0.000	—[a]
+10 g force						
Saline	127.0 ± 10.8	0.12 ± 0.02	39.6 ± 3.3	85.3 ± 9.1	0.10 ± 0.01	59.0 ± 6.2
MAP 0.3	145	0.16	34.5	76	0.09	65.8
MAP 1.0	166	0.24	30.1	110	0.14	45.5
MAP 3.0	144	0.08	22.9	9	0.01	11.1[a]
MAP 5.6	0	0.000	—	1	0.001	—[a]

[a] These responses were not used for relative cumulative frequency distributions because fewer than 25 responses were emitted.

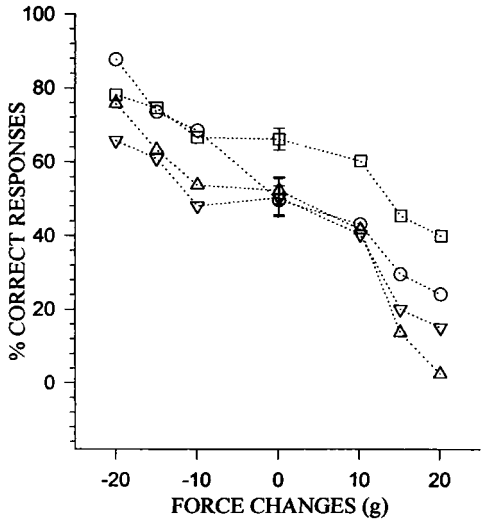

Fig. 1. Effects of changes in force requirements on accuracy. Abscissa: increases or decreases in baseline force requirements in grams. Ordinate: percentage of responses between 1.0 and 1.3 s in duration (percentage of correct responses or accuracy). Each point is a single observation in 1 rat as follows: circles = Rat 402; squares = Rat 405; triangles = Rat 408; inverted triangles = Rat 413. Baseline points at 0 show means from 10 sessions. Brackets show ±1 *SD*.

but was 66% for Rat 405. Rat 405 had the lowest baseline force requirement of the 4 rats. Figure 1 illustrates changes in accuracy of individual rats as the baseline force requirements changed. Increases in force requirements decreased the timing accuracy of all 4 rats, with larger increases in force producing larger decrements in accuracy. However, decreases in force requirements increased accuracy in all rats. Three of the 4 rats showed only slight changes in accuracy with both 10-g increases and 10-g decreases in the force requirement. Rat 402 (circles in Figure 1) was more sensitive to the 10-g decrease in force requirement than the other rats. For each rat, increasing the force requirements by more than 10 g decreased accuracy and decreasing the force requirements by more than 10 g increased accuracy. The correlation between force requirement and percentage of correct reinforced responses calculated across all 4 rats was high ($r = -.94$). This correlation occurred across a range of force requirements and across a range of percentage of reinforced responses.

Table 3 shows the effects of changing the

Table 5
(*Extended*)

Rat 408			Rat 413		
Responses	Response rate	Accuracy	Responses	Response rate	Accuracy
101.0 ± 5.3	0.12 ± 0.01	49.6 ± 2.7	91.0 ± 1.0	0.14 ± 0.01	55.0 ± 0.6
131	0.19	38.2	118	0.20	42.4
157	0.24	31.9	121	0.22	41.3
240	0.22	20.8	151	0.13	33.1
1	0.001	—[a]	0	0.000	—[a]
67.0 ± 1.7	0.08 ± 0.01	74.7 ± 1.9	78.0 ± 11.5	0.08 ± 0.04	61.6 ± 6.3
74	0.10	67.6	99	0.14	50.5
78	0.010	64.1	110	0.09	45.5
75	0.10	66.7	84	0.06	59.5
71	0.04	19.7	0	0.00	—[a]
100.7 ± 19.9	0.12 ± 0.01	51.1 ± 10.9	114.7 ± 8.6	0.15 ± 0.02	43.8 ± 3.2
207	0.18	24.2	254	0.21	19.7
258	0.29	19.4	176	0.10	21.0
219	0.26	22.8	2	0.001	—[a]
0	0.000	—[a]	0	0.00	—[a]

force requirements on the total number of responses made during the session and on the response rate for each rat. Increasing the force requirement decreased accuracy, which increased the number of responses emitted, because the session usually continued until all 50 reinforcers had been delivered. Except for Rat 408, the number of responses emitted increased as the force requirement increased. Increasing the force requirement generally increased the response rate (except Rat 408 with a 20-g increase). Accuracy was negatively correlated with the response rate ($r = -.48$) when the force requirements were increased.

When the force requirements for lever pressing were decreased, accuracy usually increased, thereby decreasing the number of responses made by all rats. Decreasing the force requirements produced small decreases in the response rate of most rats. Accuracy was negatively correlated with response rate ($r = -.85$) when the force requirements on the lever were decreased.

Figure 2 shows the relative cumulative frequency distributions of response durations for each rat during saline control sessions. A sigmoidal curve with many response durations accumulating in Bins 11 through 13 indicates accurate responding, with many responses having durations between 1.0 and 1.3 s and producing the reinforcer. Leftward shifts of the cumulative curves outside the dashed lines that encompass Bins 11 through 13 indicate relative increases in response durations too short to produce the reinforcer, and rightward shifts indicate increases in the relative frequency of response durations too long to produce the reinforcer. A decrease in slope of the sigmoidal curve (seen in later figures) occurs when the relative frequency of both longer and shorter response durations increases.

As the force requirement on the response lever increased (uppercase letters in Figure 2), the cumulative frequency distribution curves shifted upward and leftward in all rats due to the relative increase in short response durations (see Curves B and C). In contrast, decreases in the force requirements shifted the cumulative frequency distributions rightward (lowercase letters, Curves a, b, c), with more response durations falling within the vertical dashed lines indicating a higher proportion of reinforced responses. Rat 408 also

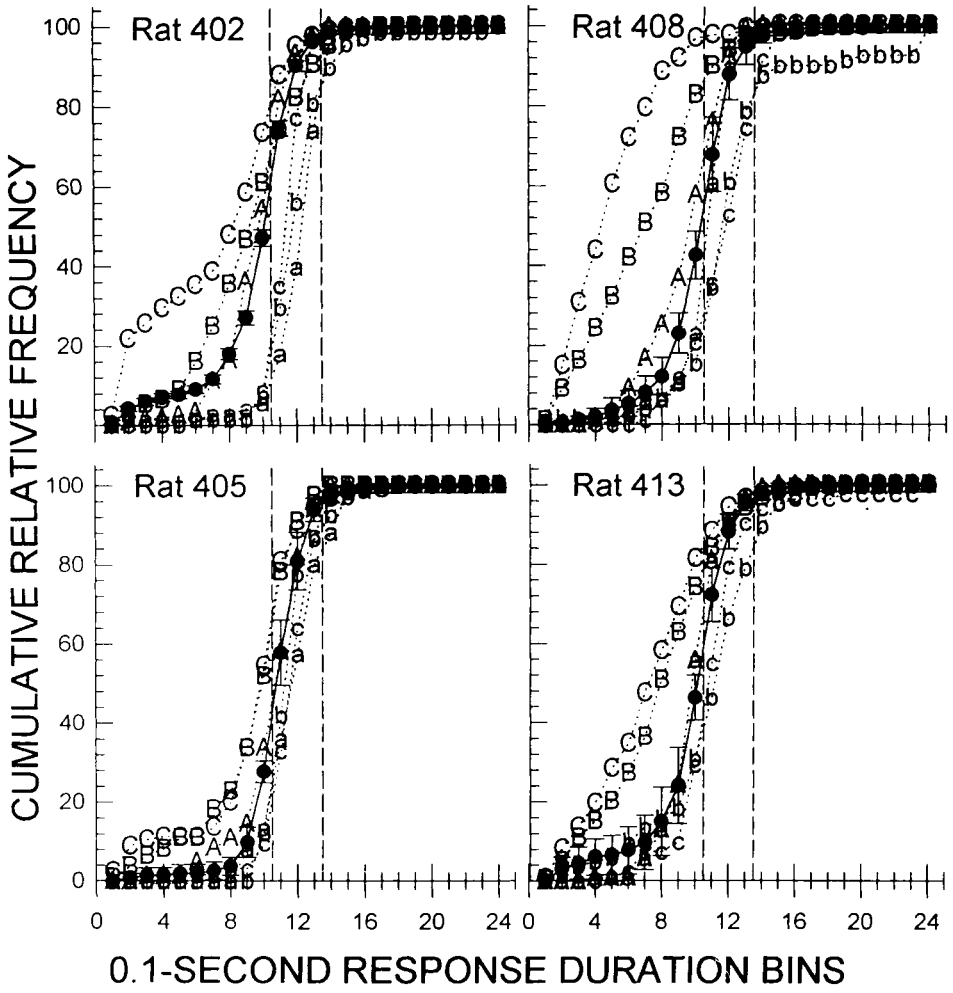

Fig. 2. Cumulative frequency distributions of response durations at different force requirements under the TRD 1–1.3-s schedule. Abscissa: response durations in 0.1-s time bins. Ordinate: cumulative number of responses in each bin as a percentage of the total number of responses. Dashed vertical lines encompass the reinforced response durations. Each drug curve represents a single observation in each rat. Each point for the control curve represents a mean based on 10 observations in each rat. Brackets show ±1 *SD*. The filled points show data from sessions at baseline force and the letters show force changes as follows: A = +10 g, B = +15 g, C = +20 g, a = −10 g, b = −15 g, c = −20 g.

showed a slight increase in the frequency of some very long response durations when the force requirements were decreased by 15 g (see Curve b), which caused the cumulative frequency curve to reach asymptote much more slowly than for other rats.

Figure 3 shows the effect of PCP on accuracy with the force required for lever pressing at the training level (baseline force), and with the requirement of either an increase in 10 g or a decrease in 15 g of force (individual-animal data are shown in Table 4). PCP produced a dose-dependent decrease in accuracy when the force requirements were the same as during training. When the force requirement was increased, accuracy after saline administration showed little change, and PCP reduced accuracy with a dose–response curve that fell slightly below and was approximately parallel to the original PCP dose–response curve before the force requirements were changed. When the force requirement for lever pressing was decreased by 15 g, the baseline accuracy after saline was higher, but the

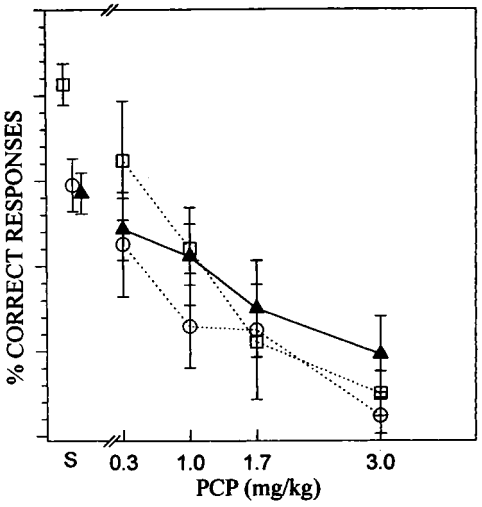

Fig. 3. Dose–response curves for the effects of PCP on accuracy under different force requirements. Abscissa: mg/kg dose of PCP, log scale. Ordinate: percentage of responses between 1 and 1.3 s in duration. Each point is an average single response in each of 4 animals. Triangles indicate baseline force requirements, circles indicate a 10-g increase in force requirements on the lever, and squares indicate a 15-g decrease in force requirements on the lever. All saline points are mean of three observations immediately preceding or following the drug administrations. Brackets show ±1 *SD*.

PCP dose–response curve for accuracy was very similar to the original dose–response curve.

Table 4 shows the effects of PCP on accuracy, on the number of responses emitted during the session, and on the response rate for each rat. With the force requirements for the lever press at the baseline level, PCP decreased accuracy, increased the total number of responses emitted, and increased the response rate. In general, these effects of PCP increased with increasing doses. Accuracy was negatively correlated with response rate ($r = -.85$) as the dose of PCP increased.

When the PCP dose–response curve was redetermined with 15-g less force required to press the lever (middle section of Table 4), the effects of PCP were very similar to those when the lever was at the baseline force, until the highest dose was reached. That is, increasing doses of PCP decreased accuracy, increased the number of responses emitted, and increased the response rate. After the 3.0 mg/kg dose of PCP, however, the number of responses emitted and the response rate decreased for Rat 413, and especially for Rat 405. There continued to be a negative correlation between accuracy and response rate ($r = -.80$) as the dose increased, if the data for Rat 405 after the highest dose of PCP were not entered into the calculation of these correlations because only a single response was made.

When the PCP dose–response curve was redetermined with an increase in 10 g of force required to press the lever (bottom section of Table 4), the effects of PCP were slightly different. Low doses of PCP (0.3 and 1.0 mg/kg) again decreased accuracy, increased the number of responses emitted, and increased the response rate, but at higher doses the total number of responses and thus the response rate decreased for 3 of the 4 rats (1.7 mg/kg for Rats 402 and 405; 3.0 mg/kg for Rat 408). These decreases after higher doses of PCP decreased the negative correlations between accuracy and response rate as the dose of PCP increased ($r = -.03$).

Figure 4 shows the individual cumulative response distributions after PCP administration for each rat at each lever-press force requirement. The top row shows the effects of PCP on the cumulative relative frequency distributions of response durations in these rats when the force requirements were the same as during training. The middle row shows the effects of decreasing the force requirements, and the bottom row shows the effects on increasing the force requirements on the relative frequency distributions of response durations after PCP. At baseline force requirements after PCP administration, the curves shift leftward showing an increase in the relative frequency of shorter response durations which become more pronounced with increasing doses of PCP. One exception to this finding is that at the lowest dose of PCP (0.3 mg/kg), there was a decrease in frequency of short response durations for Rat 405. In addition to an increase in the relative frequency of short response durations, Rat 402 produced an increase in longer response durations at the 1.7 mg/kg dose, causing the flattening of the slope of the cumulative response-duration distribution curve (Curve C). Also in this rat, at the 3.0 mg/kg dose a large increase in shorter responses shifted the curve leftward to such an extent that almost

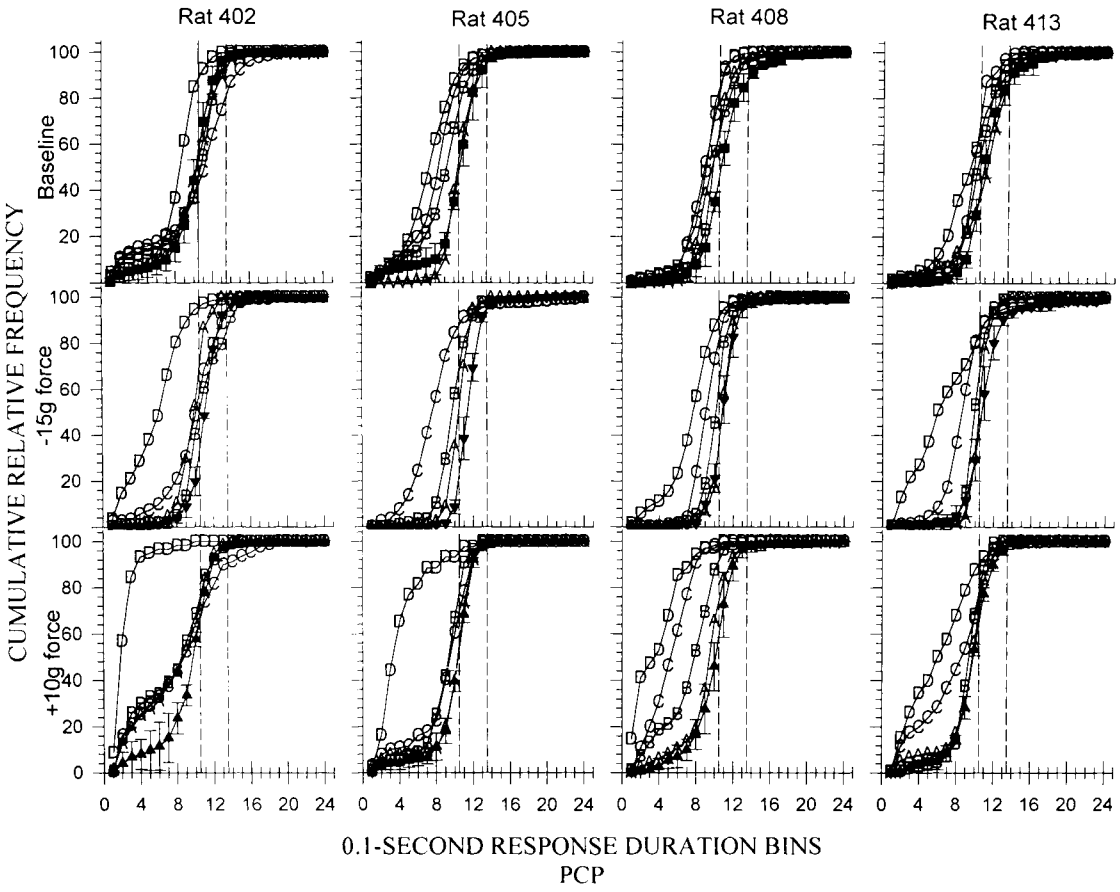

Fig. 4. Effects of phencyclidine on the cumulative relative frequency distribution of response durations with different force requirements. Abscissa: response durations in 0.1-s time bins. Ordinate: cumulative number of responses in each bin as a percentage of the total number of responses. Each PCP curve represents single observations in each rat. Each saline curve represents a mean of three observations. Brackets show ±1 *SD*. Doses are indicated in the key. Dashed vertical lines encompass reinforced response durations. Squares indicate the control baseline, inverted triangles indicate the effects of saline with the 15-g decrease in the force requirement, and triangles indicate the effects of saline with the 10-g increase in the force requirement. PCP doses are as follows: ● = saline, A = 0.3, B = 1.0, C = 1.7, D = 3.0 mg/kg.

no responses fell in the reinforced zone (Curve D).

When the force requirements were decreased by 15 g (Figure 4), distributions also shifted toward shorter response durations after PCP administration. The magnitude of the increase in short response durations was greater than under baseline force requirements. These effects became more pronounced after higher doses of PCP, at which short response durations became more frequent. Thus PCP shifted the cumulative relative response-duration distribution to the left.

When the force requirements were increased by 10 g (Figure 4), the response-duration distribution also shifted toward shorter durations after PCP aministration. Again, the magnitude of these shifts was greater than under the baseline force requirments. The degree to which the distribution shifted to the left generally increased with the dose, and after the 3.0 mg/kg dose (D curves) the shifts were particularly large.

Figure 5 shows the effect of methamphetamine on accuracy under the same three force requirements for lever pressing (individual data are shown in Table 5). There was a dose-dependent decrease in accuracy when the required force to press the lever was the

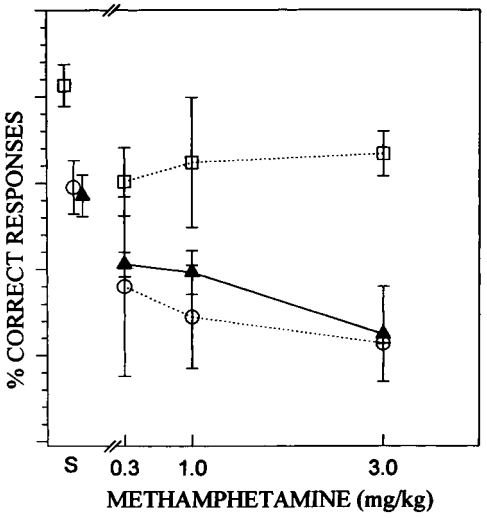

Fig. 5. Dose–response curves for the effects of methamphetamine on accuracy at different lever force requirements. Details as in Figure 3.

same as during training, although the dose–response curve was not very steep. The addition of the 10-g force requirement produced minimal change in the performance after saline administration (Figure 5), and the increased force requirement decreased accuracy only slightly after doses of methamphetamine relative to the original methamphetamine dose–response curve. However, doses of 0.3 to 3.0 mg/kg methamphetamine had little effect on accuracy when force requirements were decreased by 15 g. The effect of the highest dose of 5.6 mg/kg was omitted from this figure because this dose eliminated responding in all but 1 rat.

Table 5 shows the effects of methamphetamine on accuracy, number of responses, and response rate. With the force requirements for the lever press at the baseline level, methamphetamine produced a dose-dependent decrease in accuracy and an increase in the number of responses emitted until the 5.6 mg/kg dose was given, which almost eliminated responding in all rats. Doses of 0.3 and 1.0 mg/kg methamphetamine increased the response rate, but at the 3.0 mg/kg dose, the response rate began to decline. The correlation between accuracy and response rate was low ($r = +.15$).

When the methamphetamine dose–response curve was redetermined with 15-g less force required to press the lever (middle section of Table 5), accuracy decreased only slightly at doses lower than 5.6 mg/kg. The number of responses emitted showed some small increases after most doses, except that the highest dose (5.6 mg/kg) decreased the number of responses in all rats except Rat 408. Response rates increased slightly at the 0.3 mg/kg dose and then showed a gradual decrease with increasing doses in all rats. Accuracy was only moderately correlated with the response rate ($r = +.38$).

When the methamphetamine dose–response curve was redetermined with 10 g of additional force required to press the lever (bottom section of Table 5), accuracy decreased as the dose increased (Rats 402 and 405) or decreased at a low dose and remained decreased until responding was eliminated (Rats 408 and 413). The number of responses increased after the 0.3 and the 1.0 mg/kg doses and then decreased at higher doses, with essentially no responding occurring after the 3.0 mg/kg dose for Rat 413 and after the 5.6 mg/kg dose for all rats. Rates of responding showed a similar pattern. Accuracy was negatively correlated with the response rate ($r = -.57$).

Figure 6 shows the individual cumulative response distributions for all 4 rats after methamphetamine administration. At the baseline training force requirement, each rat showed increases in the relative frequency of short response durations that became more pronounced as the dose increased, although the effects were small for Rats 405 and 413. The 3.0 mg/kg dose also increased the frequency of response durations that were too long to produce the reinforcer. These increases in longer response durations were particularly pronounced for Rats 402 and 413. Thus, the 3.0 mg/kg dose flattened the distribution, increasing the relative frequency of response durations too short and too long to produce the reinforcer.

When the force requirements on the lever were decreased by 15 g (Figure 6), the effects of methamphetamine were attenuated in all animals except Rat 413, for which there was little effect of methamphetamine to be attenuated under baseline conditions. Methamphetamine had little effect on the cumulative response-duration distributions of Rat 413 when the lever-press requirement was at the baseline force or when an increase in force

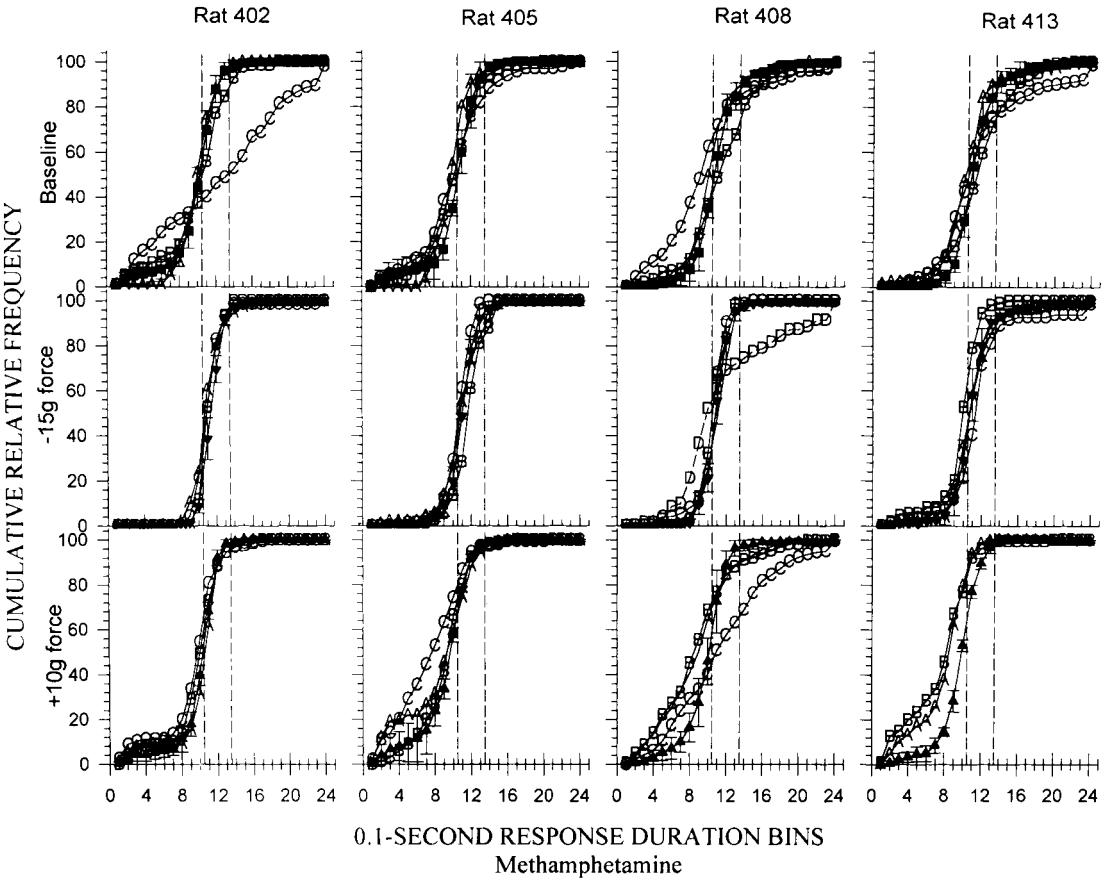

Fig. 6. Effects of methamphetamine on the cumulative relative frequency distribution of response durations with different force requirements. Details as in Figure 4, except that doses are as follows: ● = saline, A = 0.3, B = 1.0, C = 3.0, D= 5.6 mg/kg.

of 15 g was required. For Rats 402 and 405 the decreased force requirement resulted in an increased accuracy after the 3.0 mg/kg dose (C curves).

When the force requirements for responding were increased by 10 g, for all rats methamphetamine increased the frequency of short response durations. The increases in the relative frequency of short response durations were greater than when the baseline force requirement was in effect for Rats 402, 408, and 413, and about the same for Rat 405. Rat 408 also showed an increase in the frequency of long response durations after the 3.0 mg/kg dose. Thus methamphetamine produced increases in the relative frequency of short responses when the lever-press force requirements were the same as during training. When less force was required to press the lever, these effects were attenuated. When greater force was required to press the lever, the direction of the effects depended on the dose and the rat.

DISCUSSION

Fifty to 66% of the responses of rats trained to hold a lever down for at least 1.0 s but less than 1.3 s were reinforced. Most of the unreinforced responses were too short to produce the reinforcer. This finding is similar to previous reports on the patterns of responding under this TRD schedule (Hudzik & McMillan, 1994a, 1994b; McMillan et al., 1994; McMillan & Patton, 1965). It was suggested that these precisely timed responses might require the acquisition of precise motor responses to produce the reinforcer. If this is

the case, changing the force requirements on the lever might be expected to disrupt performance, perhaps by changing the proprioceptive feedback from lever presses. As expected, increases in the force requirement for lever pressing did decrease accuracy. Furthermore, this decrease in accuracy became more pronounced as the force required to press the lever increased. However, when the force requirements for lever pressing were decreased, a disruption of accuracy in responding was also expected for similar reasons. This did not occur. Decreasing the force requirements to operate the lever increased accuracy in performance under the TRD 1–1.3-s schedule. Therefore, accuracy on this timing task cannot be explained entirely on the basis of the conditioning of a precise motor response controlled by proprioceptive feedback from lever pressing.

It is also difficult to explain these results in terms of a central ''clock'' or timing mechanism for the same reasons. If the animal is producing a timed response, the duration of which is controlled by a timing mechanism presumably located in the central nervous system, it is not clear why increasing the force requirements should disrupt performance but decreasing the force requirements should improve performance.

In these experiments, accuracy appeared to be inversely proportional to the force requirements for lever pressing. Such data might suggest a relation between response effort and performance on this timing task. Perhaps a requirement for increasing effort at higher force requirements caused the lever to be released sooner, and a requirement for decreasing effort with lower force requirements caused the lever to be held down longer. This supposition is consistent with the data in Figure 2 that suggest an increase in the relative frequency of short responses that were not reinforced as the force requirement increased and a decrease in the relative frequency of these short responses as the force requirement decreased.

Additional data also suggest a relation between lever pressing and effort in making these precisely timed responses. Performance at baseline appeared to be loosely related to the force requirement in different rats. The rat that had the lowest force requirement had the highest percentage of correct responses. The other 3 rats showed nearly identical baseline accuracy, although the force required to press the lever ranged from 25 to 32 g.

It is also possible that the changes in accuracy as the force requirements changed were influenced by changes in the physical characteristics of the lever. For example, adding weight to the lever on the side of the fulcrum away from the animal might cause the microswitch to open more rapidly when the lever was released, but subtracting weight might slow the return of the microswitch to the normally open position. This might explain why the relative frequency of short responses increased with increasing force requirements and decreased with decreasing force requirements. However, it is difficult to explain why a ''sluggish'' lever return would lead to an increased reinforcement frequency after extended training with lower force requirements, and such considerations do not explain the drug effects that were observed. Furthermore, the Gerbrands lever is constructed such that the microswitch spring pushes in the same direction as the weights on the lever. Even without weights on the lever, the microswitch spring is strong enough to return to its normally open position.

Increases in force requirements did not cause the rats to decrease the total number of responses emitted or the response rate. In fact, total responses and response rate both increased at higher force requirements. The negative correlations between accuracy and both responses emitted and response rate, along with the shifts toward shorter response durations, suggest that as the force requirements increased, the proportion of responses too short to produce the reinforcer increased. This caused the total number of responses to increase, probably not so much because the response durations were shorter, but rather because the decreased frequency of reinforced responses resulted in rats having to emit more responses to obtain the 50 reinforcers within the 40-min session. Response rate might also increase due to the increased frequency of shorter responses, which results in a decreased rate of reinforcer delivery and thus less pausing to eat food pellets.

With baseline force requirements in effect, PCP decreased accuracy as a function of increasing dose. This effect occurred primarily

because of increases in the relative frequency of response durations too short to produce the reinforcer. Hudzik and McMillan (1994a) and McClure et al. (1997) also found that PCP decreased accuracy by increasing the relative percentage of short response durations using this TRD schedule.

The tendency for PCP to increase the relative frequency of short responses was potentiated both by increasing and decreasing the force required to operate the lever, although the magnitude of the effect was somewhat larger when force increases were required. Because both increasing and decreasing the force required to operate the lever increased the proportion of short response durations after PCP administration, it seems unlikely that PCP produced its effect by interacting with effortfulness of the response. Instead, PCP may have produced its effects by interacting with central nervous system timing mechanisms, such as the internal clock proposed by Church and Meck (Church, 1984; Meck, 1983; Meck & Church, 1983, 1987).

According to the internal clock concept, the ''speeding up'' of the internal clock would result in release of the lever before the minimum duration required for reinforcement had elapsed. This should occur under all force requirements, which is what was observed. Why there should be a potentiation of the increased frequency of short response durations produced by PCP with both increases and decreases in force requirements, however, is not readily explained by reference to an internal clock.

Whatever mechanism produced the effects of PCP, it was not that the total number of responses was being suppressed by PCP or that responding was extinguishing due to infrequent delivery of the reinforcer after drug. The low doses of PCP that decreased reinforcement frequency increased the total number of responses and the response rate. Changes in the reinforcement rate after drug do not appear to be a major mechanism in disrupting timing behavior under TRD schedules. For example, reinforcing only 50% of the correct responses increased accuracy under the TRD schedule, rather than decreasing it (McMillan et al., 1994).

Another possible explanation for these data is that the effects of PCP are determined by the baseline accuracy. The dose–response curves for PCP determined at different lever weights had similar shapes and slopes. The primary differences in the PCP curves are that they begin their descents from different levels of accuracy, which in turn are largely a function of the force required to operate the lever. According to this description, baseline performance is modified by changes in force requirements, but the effects of PCP are very similar at each force requirement.

Under baseline force requirements, methamphetamine also decreased the frequency of reinforced responding as a function of dose. This effect also was caused by an increased frequency of short response durations, although at high doses there was also a tendency for an increase in longer durations, indicative of a flattening of the response-duration distribution. These effects of methamphetamine are also similar to those reported previously (Hudzik & McMillan, 1994a; McClure et al., 1997). These effects of methamphetamine were attenuated when the force requirements for lever pressing were reduced. The shifts toward shorter response durations that methamphetamine produced were attenuated, and the curves relating the percentage of correct responses to the dose of methamphetamine remained relatively flat in all rats. The decrease in force requirement appeared to be protecting the rats against the methamphetamine effect. In contrast, when the force requirements for lever pressing were increased, methamphetamine again reduced the frequency of reinforcer delivery. Although the decrease was related to an increase in short response durations, the increases in long response durations were eliminated. The differences in the effects of methamphetamine as a function of lever force requirements and the individual differences among animals make a simple explanation based on the speeding up of an internal timing mechanism difficult to reconcile.

Although we are not able to explain precisely the mechanism by which the timing of these short responses occurs, nor are we able to specify exactly how the drug effects are mediated, the data were consistent across animals. The experiments illustrate the complexity of timed responding and the effects of drugs on this responding. We have shown previously that the effects of drugs on responding under TRD schedules depend on

the drug (Hudzik & McMillan, 1994a, 1994b; McClure & McMillan, 1997; McClure et al., 1997), the duration of the response being timed (McClure & McMillan, 1997; McClure et al., 1997), what the animal is required to do during timing (McClure & McMillan, 1997; McClure et al., 1997), and the schedule under which timed responses are reinforced (McMillan et al., 1994). Mechanisms such as changes in the speed of a hypothetical internal clock or changes in proprioceptive response feedback are unlikely to provide a full explanation for all of the complex interactions between drugs and timing behavior.

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